REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 6-8 were previously cancelled. Claims 10-12 are withdrawn pursuant to Applicants' election of February 6, 2008, pending allowance of the product claims under examination.

Claims 1 and 13-15 are amended to correct a typographical error. This amendment does not introduce new matter nor require a new search.

Upon entry of the foregoing amendment, claims 1-5 and 9-15 are pending, and claims 1-5, 9 and 13-15 are under examination and rejected.

II. Typographical error in the BIB sheet

Applicants acknowledge the new BIB sheet to correct the USPTO's typographical error.

III. Rejection under 35 U.S.C. § 102(e)

The rejection of claims 1-5, 9 and claims 13-15 as allegedly anticipated by Patent Application Publication No. US 2003/0115614 A1, to Kanda *et al.* ("Kanda") is maintained, for reasons of record and further supplemented at page 3-4 of the Office Action. Applicants respectfully traverse the rejection for reasons of record, and further in view of the following supplemental comments.

The present rejection relies on a theory of inherency. In particular, the Examiner notes that Applicants produce anti-HM1.24 antibodies in YB2/0 cells and that Kanda produces proteins in YB2/0 cells and that Kanda also recites that one may also produce the anti-HM1.24 antibody. Page 4 of the Office Action. The Examiner asserts that because the cell line is identical, antibody glycosylation is identical, and therefore the element missing from the claims is inherently present in Kanda.

There are two reasons, however, why Kanda fails to inherently anticipate the present rejection.

The first reason is that glycosylation is not dependent solely on the cell line, but may be altered by environmental factors, such as culture conditions. In this regard, Applicants submit herewith five references demonstrating how glycosylation, especially fucose glycosylation, is strongly affected by growth conditions:

(1) Jenkins, N. *et al.* (1994), "Glycosylation of recombinant proteins: Problems and prospects" *Enzyme Microb. Technol.*, 16, 354-364.
(2) Gawlitzek, M. *et al.* (1995), "Characterization of changes in the glycosylation pattern of recombinant proteins from BHK-21 cells due to different culture conditions" *J. Biotechnol.*, 42, 117-131.
(3) Schweikart, F. *et al.* (1999), "Rapid structural characterisation of a murine monoclonal IgA α chain: heterogeneity in the oligosaccharide structures at a specific site in samples produced in different bioreactor systems" *J. Biotechnol.*, 69, 191-201.
(4) Restelli, V. *et al.* (2006), "The Effect of Dissolved Oxygen on the Production and the Glycosylation Profile of Recombinant Human Erythropoietin Produced From CHO Cells" *Biotechnol. Bioeng.*, 94(3), 481-494.
(5) Covic, A. *et al.* (2007), "Biosimilars: recent developments" *Int. Urol. Nephrol.*, 39:261-266.

Not only does the art demonstrate the identical cell lines do not result in identical glycosylation, but Kanda actually demonstrates a different pattern of glycosylation to that observed in Applicants' specification. *See* remarks below.

Accordingly, even if the identical antibody is being produced from the identical cell line, one does not *necessarily* observe identical glycosylation. A result *must necessarily* flow for it to be inherently present in the prior art. MPEP § 2112 recites:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed

> rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

MPEP § 2112, markings in original. Moreover, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), cited in MPEP 2112, markings in original. *See also In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

Because identical glycosylation does not necessarily flow from the use of an identical cell line, the missing element is not inherently present in Kanda. Kanda cannot, therefore, anticipate the present claims.

The other reason that Kanda does not inherently anticipate the claims is that the present assertion of inherency is specifically contradicted by facts provided by Kanda. The inherent teachings of a prior art reference is a question of fact. *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). *See also In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983), MPEP § 2112.

Thus, if the inherent existence of a missing feature may be asserted based on reason, even if one may reasonably assert that a missing feature is asserted, it may be rebutted by factual evidence. Thus, while reason may suffice to assert that a missing element is inherently present, such assertions, based solely on theory, must necessarily fail in the face of contradictory evidence.

The claimed anti-HM1.24 antibody comprises a sugar chain which includes N-glycoside-linked sugar which has a basic structure of Manβ1-4GlcNAcβ1-4GlcNAc-PA wherein said sugar chain does not contain α1,6 core fucose, but contains a bisecting N-acetylglucosamine (GlcNAc) which is bound with a β1,4-linkage on the mannose (Man) of the basic structure. The present specification identified bisecting GlcNAc chains in 11.3% of all sugar chains. *See* Table 1, page 19. Of the bisecting GlcNAc sugar chains, 29% were fucose-free. *Id.*

Kanda, by contrast, identified only a very small amount of bisecting GlcNAc sugar chains (*see* Kanda, pages 55, 56 and Figure 30), and all of this was fucosylated. That is, Kanda specifically identified the sugar chains present on antibodies in cultured cells, and failed to find the sugar chains claimed by Applicants in claim 1, or the species recited in claims 13, 14 or 15. Kanda demonstrates that the claimed species was absent as "a question of fact," under *In re Napier*, 55 F.3d 610.

Applicants' situation is, therefore, clearly distinct from *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999), cited by the Examiner. Applicants are not claiming "a previously unappreciated property of a prior art composition," *id.*, because the prior art composition *has* been analyzed, and found to be different. Applicants' situation may also be distinguished from *In re Crish,* 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), cited in MPEP 2112, where the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. It follows that if the prior art *had* sequenced the DNA and found a sequence different to that claimed by Crish, there would not have been inherency because the prior art demonstrates the opposite, as a matter of *fact.* Applicants situation is, therefore, like the counterfactual situation in Crish, which should not lead to a finding of inherency.

Applicants therefore believe that the present claims are not inherently anticipated by Kanda, because the assertion of inherency relies on an assumption that identical glycosylation necessarily flows from the practice of Kanda's specification, when this assumption is shown

to be false in the literature and by a comparison of results reported by Kanda and Applicants. Moreover, the assertion of inherency is entirely reliant on theory and therefore falls in the face of contradicting factual evidence. Applicants respectfully assert that the rejection of claims 1-5, 9 and 13-15 is overcome, and seek reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants believe that the rejection of claims 1-5, 9 and 13-15 is overcome. Because the composition claims are believed to be allowable, withdrawn claims 10-12 are eligible for rejoinder and examination. Early notice to this effect is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Any incorrect or missing payment should also be charged to the deposit account. If any extensions of time are needed, Applicants hereby petition under 37 C.F.R. §1.136 for such extension and authorize payment from the deposit account.

Respectfully submitted,

Date Oct. 20, 2009

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